AMENDMENTS TO THE DRAWINGS:

Attached are 6 replacement sheets of drawings with changes to Figs. 1A-1F, respectively. These sheets replace the 6 sheets of drawings filed September 26, 2005. In these 6 replacement sheets, the figure legends under the results have been deleted.

Also attached are 12 annotated sheets of the drawings as originally filed, marked to show the changes made (in addition to those changes described in Applicants' responses dated August 25, 2004, September 26, 2005, and March 28, 2006) relative to Figs. 1A-1F submitted herewith and Figs. 2A-7B submitted on September 26, 2005. Specifically, the annotated sheets show the deletion of certain hand-written notes from the original figures.

Attachments: Replacement Sheets (6)
Annotated Sheets Showing Changes (12)

REMARKS

Claims 54-71 were pending. New claims 72 and 73 has been added, and claims 54, 55, 70 and 71 have been amended to clarify the invention. Specifically, the subject matter of dependent claim 56 has been incorporated into each of claims 54 and 55 and claim 56 has been canceled without prejudice. Claims 70 and 71 have been amended to avoid depending on a canceled claim. Support for new claims 72 and 73 is found in the specification, for example, at page 32, lines 4-6.

1. STATEMENT OF THE SUBSTANCE OF THE INTERVIEW

Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. § 713.04, Applicant presents this statement of the Substance of the Interview in connection with the telephone interview of January 16, 2007 ("the Interview") among Examiner Ewoldt, Supervisory Patent Examiner Christina Chan, Attorney for Applicant Adriane M. Antler, Applicant Pramod K. Srivastava, and Daniel L. Levey, Ph.D. (of Antigenics, Inc., assignee).

In the Interview, Dr. Antler explained why each of the rejections in the Office Action should be withdrawn, essentially as set forth in the remarks herein below.

Regarding the rejection under 35 U.S.C. § 112 for lack of enablement, Examiner Ewoldt stated that he would consider withdrawing the § 112 rejection for lack of enablement in view of Applicant's remarks when he has the filed written response to the Office Action.

In response to a question from Supervisory Patent Examiner Chan regarding using the same dosage in both mice and humans, Dr. Srivastava explained why there was no reasonable expectation of having to extrapolate the effective dose for a human proportionately by weight/surface area from the effective dose in mice. In particular, Dr. Srivastrava explained that dosage is usually extrapolated in order to achieve certain concentrations of the administered drug in the blood of an animal. However, what makes the present case differ from the usual situation is that the present application deals with modulating an immune response, which occurs not in the blood but in the lymph nodes. The architecture of lymph nodes is the same, for example, in mice and humans. Dr. Srivastava further explained that the lack of a need to extrapolate dosages based on weight/surface area has been shown regarding the low dose immunostimulatory effect of hsps, since clinical trials are being conducted using the same 5-20 μg amount in humans as had been administered in mice.

Regarding the rejections under 35 U.S.C. § 112 for new matter, Examiner Ewoldt stated that he will reconsider the rejections in view of the explanations and support in the specification cited by Dr. Antler.

2. DRAWINGS

The Examiner stated that the Drawings filed September 26, 2005 remain unacceptable and have not been entered because in some cases, the substance of the Drawings has been changed. In particular, the Examiner alleged that the handwritten notes in the drawings have been removed, thus deleting information, and that the legends of Figures 1 and 2 have been changed, adding information.

With respect to the handwritten notes in the original drawings, Applicants hereby request that all handwritten notes be deleted as indicated on the attached annotated copies of the original drawings, marked "Annotated Sheets." Applicants submit that the hand-written notes are not necessary to understand the figures or the results of the experiments represented by the figures in view of the information presented in the Brief Description of the Figures at pages 5-6 of the specification, in the figure legends, and in the examples of Section 6 at pages 38-41 of the specification. Accordingly, Applicants respectfully request deletion of the handwritten notes.

With respect to Figures 1 and 2, the Examiner alleged that the original legends identified only 4 colors/patterns while the legends of the Drawings filed September 26, 2005 identify 6 colors/patterns. With respect to Figure 1, Applicants first note that only 5, not 6, colors/patterns are identified in the legend of the Drawings submitted September 26, 2005. Each of these 5 colors/patterns was present in the original drawings. However, one pattern was omitted from the description of Figure 1 at page 5, lines 23-28 of the specification (hatched lines = hemorrhagic area) and two patterns/colors are described in slightly different terms in the specification at page 5, lines 23-28, and in the legend of Figure 1, *i.e.*, the specification denotes "speckles" as "graft tissue red/inflamed, while the legend denotes this pattern as "less healthy area," and the specification denotes "black" as "graft tissue dead" while the legend denotes this color as "necrotic." Applicants do not believe that these differences between the description of the figure in the specification and the legend of Figure 1 constitute new matter. However, in order to expedite prosecution of the subject application, the legends to Figures 1A-1F have been deleted from the figures, rendering the objection

moot. Accordingly, six sheets marked "Replacement Sheets" 1A-1F are submitted herewith. These sheets are identical to the sheets marked 1A-1F of the Drawings submitted September 26, 2005 except that the figure legends have been deleted from each sheet.

With respect to the legend of Figure 2, Applicants note that each of the 6 colors/patterns identified in the legend was present in the original drawings and each is identified in the description of Figure 2 at page 6, lines 11-18, of the specification. Accordingly, Applicants submit that the legend of Figure 2 of the Drawings does not constitute new matter and respectfully request that this objection be withdrawn.

In view of the above, Applicants submit that the amended Drawings submitted herewith do not improperly omit information or contain new matter, and respectfully request that the Examiner accept and enter the Drawings in the file of this application.

3. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT, SHOULD BE WITHDRAWN

The Examiner rejected claims 54-71 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the relevant art to make and/or use the claimed invention. The Examiner maintained his previous view that the specification is enabling only for the specific embodiment given in Example 6 of the specification. Specifically, the Examiner alleged that the specification is enabling only for a method of inhibiting graft rejection of a skin graft of BALB/cJ (donor) skin transplanted onto a C57BL/6 (recipient) mouse, the method comprising administering (subcutaneously) to the recipient mouse 100 micrograms of gp96 purified from a donor tissue source ten days prior to transplantation followed by a repeated administration of the gp96 three days prior to transplantation.

In support of his rejection, the Examiner reiterates the allegations made in the previous Office Action. In response, Applicants respectfully submit that some of the Examiner's allegations no longer apply to the pending claims and that the rest do not support a rejection of the pending claims under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants respond to each of the Examiner's allegations in the Office Action in the following paragraphs.

With respect to dependent claim 56, Applicants note that this claim has been canceled and the subject matter of claim 56 has been incorporated into the independent claims, 54 and 55.

First, Applicants note that the independent claims as amended, 54 and 55, each recite a method of inhibiting rejection of a graft *in a mammal in need thereof* comprising administering to the mammal *a dose, effective to inhibit graft rejection,* of a composition comprising purified complexes, each complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, and wherein *the heat shock protein is a member of the hsp90 family* of heat shock proteins, and wherein *the amount of the complexes present in the composition is 100 μg or more*. Claim 54 further specifies that the composition is administered *after* the cells, tissue, or organ is grafted. Claim 55 further specifies that the method comprises administering to the mammal a sample of cells or tissue obtained from the cells, tissue, or organ donor prior to administration of the composition, and wherein said composition is administered prior to the cells, tissue, or organ being grafted to the mammal.

3.1. The Evidence in the Specification and that is Submitted by Applicants Overcomes Any Uncertainty in the Art

The Examiner alleged that "little is known regarding treating or preventing graft rejection by administering heat shock proteins" which have been shown in the art to be immunostimulatory in other contexts (see the Office Action at p. 3, para. 3). Applicants do not dispute the surprising and unexpected nature of their discovery that heat shock proteins have immunosuppressive properties. However, Applicants submit that the specification fully enables the skilled artisan to practice the claimed methods because the specification teaches how to obtain or make hsp90 family member stress proteins for use in the claimed methods and how to administer the hsp90 family members to inhibit graft rejection. Specifically, the specification teaches specific protocols for purifying the hsp90 family members gp96 and hsp90, *e.g.*, in Section 5.2.1, at pages 13-16 and pages 19-20, and for producing recombinant hsp90 family members, *e.g.*, in Section 5.2.2 at pages 20-23. The specification also provides guidance regarding the effective dosages of hsp90 family members for use in the claimed methods, including the at least 100 microgram amount specified in the claims, *e.g.*, at page 31, line 30 to page 32, line 3 (discussed in more detail below in Section 3). The specification further provides guidance regarding the timing and routes of administration of hsps for inhibiting graft rejection, see *e.g.*, the specification at page 36, lines 26-36 (teaching the administration of hsp after transplantation of the graft, *i.e.*, according to the method of pending claim 54); page 37, lines 13-25 (teaching the administration of hsp after pre-treatment with a donor-derived cell or tissue sample and prior to transplantation of the graft,

i.e., according to the method of claim 55); and page 31, line 17 to page 32, line 18 (dosages and routes of administration). Finally, the specification provides a working example of the claimed methods in a well-known animal model of graft rejection, the mouse skin transplantation model (see the specification at p. 38-41).

The Examiner also quoted from Pockley 2001 "Heat shock proteins, anti-heat shock protein reactivity and allograft rejection," *Transplantation* 71:1503-1507 ("Pockley") (of record as previously cited by Examiner), in support of his contention that "the invention of the instant claims [is] unpredictable" (see the Office Action at p. 4, para. 3).

In response, Applicants submit that Pockley does not address the subject matter of the claimed invention, namely the immunosuppressive effects of purified hsp-peptide complexes administered to a graft recipient. Instead, Pockley addresses the role of *endogenous* heat shock proteins in immunity and autoimmunity. Nonetheless, Applicants further submit that Pockley does not give sufficient reason to doubt the enablement of the claimed methods in view of the evidence submitted by Applicants which demonstrates the immunosuppressive effects of gp96, an hsp90 family heat shock protein, in five different animal model systems, *i.e.*, in a tumor transplantation model, in the non-obese diabetic ("NOD") model (a mouse model of autoimmune diabetes), in two types of EAE (experimental autoimmune encephalomyelitis, a model for multiple sclerosis) and in a mouse model of allograft rejection (the skin transplantation model), each of which is discussed in Section 2 below. Moreover, while Pockley addresses the evidence for a negative impact of heat shock proteins on graft outcome, Pockley also notes and emphasizes the protective effects of heat shock proteins on graft outcome (see *e.g.*, Pockley at p. 1505, col. 1, concluding sentence). Thus, Applicants submit that Pockley, while acknowledging the uncertainty regarding the role of heat shock proteins in graft outcome, nevertheless fails to provide sufficient evidence to doubt the enablement of the claimed methods in view of the supporting data provided by Applicants which demonstrates a protective effect for gp96 on graft outcome, as discussed below.

In view of the above, Applicants submit that the claimed methods for using heat shock proteins to inhibit graft rejection are fully enabled by Applicants' disclosure.

3.2. The Evidence Submitted by Applicants Shows the Immunosuppressive Activity of High Dose hsp90 Family Members in Various Contexts

The Examiner asserted that the scope of the claims is broad because the claims "encompass the claimed method employing all HSPs (except hsp60 and cpn10)" (see the Office Action at p. 3, para. 4). The Examiner also asserted that the specification lacks enablement for the use of hsp70 family members in the claimed methods and that such support was not provided by WO 02/072133 (previously submitted by Applicants) (see the Office Action at p. 4, para 1-2).

Applicants have presented the declaration of Dr. Srivastava, (see paras. 11,12), Chandawarkar et al., 2004 "Immune modulation with high-dose heat shock protein gp96: therapy of murine autoimmune diabetes and encephalomyelitis," *Int. Immunol.* 16: 615-624 ("Chandawarkar 2004") (ref. CS of Applicants' Supplemental Information Disclosure Statement filed August 25, 2004), and Kovalchin *et al.*, 2006 "In vivo treatment of mice with heat shock protein, gp96, improves survival of skin grafts with minor and major antigenic disparity," *Transplant Immunol.* 15:179-195 ("Kovalchin") (ref. CV of Applicants' Supplemental Information Disclosure Statement dated March 28, 2006), all of which demonstrate that high doses of gp96-peptide complexes are immunosuppressive and that this effect is not dependent on the source of the gp96-peptide complexes (and thus is not dependent on the identity of the peptides complexed to the hsp).

Regarding Chandawarkar 2004, data were presented showing that high dose (100 μg gp96-peptide complexes) suppresses tumor immunity, while a 10 μg dose does not. In particular, gp96-peptide complexes were shown to suppress an immune response directed against a tumor where an immunizing dose (10 μg) of gp96-peptide complexes isolated from tumor tissue is combined with an excess (90 μg) of gp96-peptide complexes isolated from liver tissue (see Declaration of Dr. Srivastava at para. 11). Thus, a dose of 10 μg of gp96-peptide complexes from tumor tissue is able to effectively stimulate an immune response in mice against the tumor, but the same dose combined with 90 μg of gp96-peptide complexes from a non-tumor tissue suppresses that immune response, allowing the tumor to grow. A 100 μg dose of gp96-peptide complexes isolated from the tumor was also immunosuppressive in that it allowed the tumor to grow (see Chandawarkar 2004, p. 616, col. 2). Data was also presented in Chandawarkar 2004 showing that a high dose (100 μg) of gp96-peptide complexes, but not a low dose (10 μg), suppresses the development of diabetes in the NOD mouse model, which is a model of autoimmune diabetes (see also Declaration of Dr. Srivastava at para. 12). The 100 μg dose was effective regardless of whether the gp96-peptide complexes were isolated from pancreas or liver tissue. Chandawarkar 2004 also

shows that high dose gp96-peptide complexes is immunosuppressive in two forms of EAE (experimental autoimmune encephalomyelitis, a model of multiple sclerosis) (see Chandawarkar 2004 at p. 618, Fig. 3). Thus, these results demonstrate that gp96-peptide complexes are immunosuppressive at high doses and that this effect is specific to the heat shock protein *per se*, since the effect was observed regardless of the tissue source of the gp96-peptide complexes and thus the identity of the peptides to which the gp96 was complexed (see Declaration of Dr. Srivastava at paras. 12-14). Chandawarkar 2004 also shows that the immunosuppressive activity of high dose gp96-peptide complexes is mediated by $CD4^+$ T cells and could be adoptively transferred (see Chandawarkar 2004 at p. 619; p. 621, col. 2).

The data in the specific examples of Applicants' specification are consistent with the data described above. In particular, the data in Applicants' specification demonstrates that gp96-peptide complexes are immunosuppressive at high doses and that this effect is specific to the heat shock protein *per se*, because the effect was observed regardless of whether the gp96-peptide complexes were isolated from the graft tissue (skin) or from a non-graft tissue (*i.e.*, liver) (see Declaration of Dr. Srivastava at para. 13). The examples described at pages 38-41 of the specification teach that graft rejection is inhibited in skin graft recipients by administration of high doses (at least 100 μg) of gp96-peptide complexes obtained from donor tissue (but not necessarily from the same tissue type as the graft, *i.e.*, gp96-peptide complexes from donor liver worked as well as gp96-peptide complexes from donor skin, see *e.g.*, the specification at p. 39, lines 6-37). Thus, the foregoing shows that high dose gp96-peptide complexes are immunosuppressive in a large variety of contexts, consistent with the demonstrated mechanism in Chandawarkar - that the immunosuppressive activity is mediated by $CD4^+$ T cells.

The Examiner contended that the results of Experiment 2 at pages 40-41 of the specification do not support the use of all gp96 family members in the claimed methods because in that experiment, rat gp96 did not inhibit rejection of the skin graft from donor mice. The Examiner asserted that "the most likely conclusion to be drawn from the limited data is that gp96 must derive from the same genetic source as the graft" (see the Office Action at p. 3, para. 4). Applicants respectfully disagree with this characterization of the results of Experiment 2. The Examiner is referring to the experiment described in the specification at page 40, line 1 to page 41, line 19. In that experiment, the recipient mice were divided into 10 treatment groups as follows:

1. No treatment;
2. Buffer (administered intradermally, "i.d.");
3. Buffer (administered subcutaneously, "s.c.");
4. 1 microgram donor mouse gp96 (i.d.);
5. 10 micrograms donor mouse gp96 (i.d.);
6. 10 micrograms donor mouse gp96 (s.c.);
7. 100 micrograms donor mouse gp96 (i.d.);
8. 100 micrograms donor mouse gp96 (s.c.);
9. 200 micrograms donor mouse gp96 (s.c.);
10. 10 micrograms rat gp96 (i.d.);

The results showed that graft rejection was inhibited in the recipient mice of groups 8 and 9, with the most effective inhibition occurring in group 9, which also received the highest dose of donor mouse gp96-peptide complexes (see the specification at p. 41, lines 11-19). Applicants point out that the 10 microgram dose gave negative results in both of the other two groups in which it was used, and for which the gp96-peptide complexes were from donor *mouse* (see results for groups 5 and 6). In other words, the 10 microgram dose of gp96-peptide complexes failed to inhibit graft rejection *independent of whether it was from mouse or rat*. These data are consistent with Applicants interpretation that the 10 microgram dose is simply too small a dose to be immunosuppressive, because the 10 microgram dose of mouse or rat gp96-peptide complexes in groups 5, 6, and 10 all did not work, regardless of species, whereas the 100 microgram and 200 microgram doses (groups 8 and 9) did work. This interpretation is also shown to be correct by Chandawarkar 2004, which shows, as discussed above, that 100 μg of gp96-peptide complexes, but not 10 μg, is immunosuppressive in the tumor transplantation model and in an NOD model.

Also, data in Kovalchin show that the invention works as claimed. In Kovalchin, a high dose of gp96-peptide complexes improved survival of skin grafts, with minor or major antigen disparity, in three different types of experiments. Moreover, Applicants' interpretation of the data is shown to be correct by Kovalchin. Kovalchin demonstrates that, contrary to the Examiner's contention, the genetic source of the gp96-peptide complexes used to inhibit graft rejection does not have to be of the same genetic source as the graft, including strain differences.[1] The Examiner's attention is directed to the results depicted in Figures 1 and 3. In each of these experiments, gp96-peptide complexes purified from the liver of female mice (see Kovalchin at p. 180, col. 1, para. 3) were used to inhibit the rejection of skin

[1] Although Kovalchin does not expressly refer to "complexes" of gp96 and peptide, Kovalchin notes at p. 184, col. 1, last paragraph that "it is not technically feasible to denude gp96 preparations from associated peptides without denaturing the protein . . ." Thus, it is evident that the gp96 used by Kovalchin was in the form of gp96-peptide complexes.

grafts from male mice onto female recipients, even females that had previously rejected the male skin grafts. Although the male and female mice were of the same strain (C57BL/6), the difference in sex between the donors and recipients ensured minor antigen disparity between the source of the gp96-peptide complexes and the donor graft tissue. Thus, the gp96-peptide complexes used in these experiments cannot be considered "of the same genetic source" as the graft. Nevertheless, a 100 microgram dose of gp96-peptide complexes was effective to inhibit graft rejection in these experiments, demonstrating that the gp96-peptide complexes need not be from the same genetic source as the graft. Kovalchin also shows that a 100 microgram dose of gp96-peptide complexes inhibited graft rejection even where there was major antigen disparity, due to skin grafts from female BALB/C donors being transplanted to female C57BL/6 recipients. Importantly, Kovalchin also states that inhibition of rejection was strain and tissue independent (see Kovalchin at p. 184 col. 1 para. 3). Kovalchin specifically states that the Examiner's contention regarding strain specificity is incorrect:

> In order to access whether differences existed in the effects of different sources of gp96, we treated recipient mice with gp96 obtained from either C57 or BALB/c harvested livers, skin or even tumors (methocholanthrene-induced [Meth-A] sarcoma,) (data not shown). The gp96 was equally effective at prolonging graft survival regardless of the source it was purified from.
>
> (Emphasis added). (Kovalchin at p. 184, col. 1, para. 3).

Thus, as Kovalchin notes, while the ability of gp96-peptide complexes to elicit an anti-tumor immune response is "exquisitely source-specific" (*i.e.*, only tumor-derived gp96-peptide complexes are able to elicit an immune response against tumor cells in the tumor transplantation model system), "the immunosuppressive activity elicited by HDgp96 [high dose gp96-peptide complexes] is not" (Kovalchin at p. 184 col. 1 para. 3). Thus, the Examiner's contention that the 10 μg dose of gp96-peptide complexes did not work because the gp96-peptide complexes were not derived from the same genetic source as the graft is simply incorrect.

3.3. The Specification Enables the Use of hsp90 Family Members

The Examiner also alleged that the specification lacks enablement for the use of hsp90 family members, other than gp96, in the claimed methods because in the example in the specification rat gp96 was not effective in inhibiting graft rejection (see the Office Action at p. 5, para. 3). The Examiner is referring to the experiment discussed above and described

in the specification at page 40, line 1 to page 41, line 19. Specifically, the Examiner alleged that the results for group 10, in which the recipient mice received 10 micrograms of *rat* gp96 which failed to inhibit graft rejection, "demonstrates that Applicant's [sic] assertions are simply incorrect" regarding there being a reasonable expectation that all hsp90 family members will be immunosuppressive based on their structural similarity (see the Office Action at p. 5, paras. 2 and 3). However, as discussed above, the 10 microgram dose gave negative results in both of the other two groups in which it was used, and for which the gp96-peptide complexes were from donor *mouse* (see results for groups 5 and 6). In other words, the 10 microgram dose of gp96-peptide complexes did not inhibit graft rejection, *independent of whether it was from mouse or rat*. These data do not support the Examiner's contention that the negative result for rat gp96-peptide complexes demonstrates that all hsp90 family members are not immunosuppressive. To the contrary, Applicants submit that the reasonable interpretation of these results is that the 10 microgram dose is simply too small a dose to be immunosuppressive, because the 10 microgram dose of mouse or rat gp96-peptide complexes in groups 5, 6, and 10 all did not work, regardless of species, whereas the 100 microgram and 200 microgram doses (groups 8 and 9) did work. Moreover, the Examiner's contention regarding a genetic source requirement for the gp96-peptide complexes has been shown to be incorrect by the discussion hereinabove, and also in view of Chandawarkar 2004 and Kolvachin. The negative result for rat gp96-peptide complexes is therefore not inconsistent with Applicants' assertion that the high degree of sequence homology among the members of the hsp90 family lends itself to a reasonable expectation that an activity identified for a given hsp90 protein, such as gp96, would be shared by other members of the same family. Rather, Applicants' data shows that routine experimentation can be used to determine an appropriate dosage for use in the claimed methods. This interpretation is further supported by the data provided in Kovalchin, discussed above, which demonstrates that a "high dose," *i.e.*, 100 μg, of gp96-peptide complexes is effective to inhibit allograft rejection in a mouse skin transplantation model.

The specification enables the use of gp96 as well as other members of the hsp90 family, of which gp96 is a member, due to the high level of sequence conservation within the family, as discussed in para. 15 of the Declaration of Dr. Srivastava. There is a minimum of 98% identity among human, rat and murine hsp90 and a minimum of 47% amino acid sequence identity between human gp96 and hsp90 of rat, murine and human species (see Declaration of Dr. Srivastava at para. 15). Applicants maintain that the specification fully

enables the skilled worker to practice the claimed methods using any hsp90 family member since members of the hsp90 family are expected to have very similar activities in view of the high degree of sequence conservation among the members of the hsp90 family, which lends itself to a reasonable expectation that the activity identified for a given hsp90 family protein, such as gp96, would be shared by other members of the same family (see Amendment dated March 28, 2006 at pages 9-10, and the Declaration of Dr. Srivastava filed on August 25, 2004 at para. 15). In particular, (1) members of the hsp90 family are expected to have very similar activities in view of their high level of structure/sequence conservation; and (2) the immunosuppressive effects of gp96-peptide complexes are not dependent on the tissue source of the gp96, indicating that the effects are specific to the heat shock protein itself (Declaration of Dr. Srivastava at para. 15). Thus, Applicants maintain that it is reasonable to expect that hsp90 family members other than gp96 will have similar immunosuppressive activity as that demonstrated for gp96 by the examples in the specification and the data presented in the Declaration of Dr. Srivastava and in Chandawarkar 2004 and Kovalchin, in view of the high level of sequence conservation among hsp90 family members.

3.4. Disclosure Regarding Effective Dose

The Examiner alleged that there is insufficient disclosure in the specification regarding the appropriate dose of hsp to enable the claimed methods for use in a mammal other than a mouse (see the Office Action at p. 3, para. 5, and at p. 4, para. 5 to p. 5 para. 1). The Examiner contended that the appropriate dose for a human would be in the range of 300,000 to 600,000 micrograms based on the teaching in the specification that an effective dose for a 20 to 25 gram mouse is 100 to 200 micrograms, since "a human is roughly 3000 times the size of a mouse." The Examiner further noted that such a dose is not disclosed in the specification.

Applicants respectfully disagree with the Examiner's premise that the effective dose for a human must be extrapolated proportionately by weight from the effective dose in mice. To the contrary, Applicants submit that the appropriate dose for a human is expected to be much lower than that predicted by extrapolation from mice based on body weight or surface area. This is taught by the specification at page 31, line 31 to page 32, line 3, which states that "[*s*]*imilar high doses of 100-200 μg, or more than 200 μg*, of hsp may also be effective in the treatment of larger mammals, including humans" (emphasis added). See also U.S. Patent No. 6,017,540, issued January 25, 2000, at col. 12, lines 44-65 (teaching that the

effective doses of hsp are much smaller than those that would be predicted from prior art methods of extrapolation, *e.g.*, based on surface area) (submitted herewith as ref. CX of Applicants' Supplemental Information Disclosure Statement).

In the telephone interview of January 16, 2007 ("the Interview") among Examiner Ewoldt, Supervisory Patent Examiner Christina Chan, Attorney for Applicant Adriane M. Antler, Applicant Pramod K. Srivastava, and Daniel L. Levey, Ph.D. (of Antigenics, Inc., assignee), Dr. Srivastava explained that when measuring the immune response of a vaccine, there is no reasonable expectation of having to extrapolate the effective dose for a human proportionately by weight/surface area from the effective dose in mice (see, the instant Amendment at p. 6, Statement of the Substance of Interview). In particular, Dr. Srivastrava explained that dosage is usually extrapolated in order to achieve certain concentrations of the administered drug in the blood of an animal. However, what makes the present case differ from the usual situation is that the present application deals with modulating an immune response, which occurs not in the blood but in the lymph nodes. The architecture of lymph nodes is the same, for example, in mice and humans. Dr. Srivastava further explained that the lack of a need to extrapolate dosages based on weight/surface area has been shown regarding the low dose immunostimulatory effect of hsps since clinical trials are being conducted using the same 5-20 μg amount in humans as had been administered in mice.

By way of exemplary evidence of the foregoing, Applicants direct the Examiner's attention to to the following references: Tamura *et al.*, 1997 "Immunotherapy of Tumors with Autologous Tumor-Derived Heat Shock Protein Preparations," *Science* 278(5335):117-120 ("Tamura") (ref. DB of Applicants' Supplemental Information Disclosure Statement filed herewith), Sato *et al.*, 2001 "Immunotherapy using heat-shock protein preparations of leukemia cells after syngenic bone marrow transplantation in mice," *Blood.* 98(6):1852-1857 ("Sato") (ref. DA of Applicants' Supplemental Information Disclosure Statement filed herewith), Yedavelli *et al.*, 1999 "Preventative and therapeutic effect of tumor derived heat shock protein, gp96, in an experimental prostate cancer model," *Int. J. Mol. Med.* 4(3):243-248 ("Yedavelli") (ref. DC of Applicants' Supplemental Information Disclosure Statement filed herewith), Belli *et al.*, 2002 "Vaccination of Metastatic Melanoma Patients With Autologous Tumor-Derived Heat Shock Protein gp96-Peptide Complexes: Clinical and Immunologic Findings," *J. Clin. Onco.* 20:4169-4180 ("Belli") (ref. CU of Applicants' Supplemental Information Disclosure Statement filed August 25, 2004), Mazzaferro *et al.*, 2003 "Vaccination with Autologous Tumor-derived Heat-Shock Protein Gp96 after Liver

Resection for Metastatic Colorectal Cancer," *Clin. Cancer. Res.* 9(9):3235-3245 ("Mazzaferro") (ref. CZ of Applicants' Supplemental Information Disclosure Statement filed herewith), all of which have experimental data demonstrating that a dose of gp96-peptide complexes in the range of 2.5 μg to 100 μg is effective in producing an immune response for the treatment of caner in mice, rats, and humans.

Tamura shows that five weekly treatments of 20 μg of gp96-peptide complexes, derived from a metastatic lung cancer cell line (D122 cells) and injected into the footpads of mice resulted in reduced growth rate of the primary footpad tumor and also resulted in reduced lung metastases (see Tamura at p. 117, col. 3 to p. 118, col. 1; Fig. 1). Tamura tested the efficacy of gp96-peptide complexes in another therapy protocol in which the D122 lung cells were injected into the footpads of naïve mice and after a tumor grew to 5 mm in diameter, the tumor was surgically removed. All the mice died of metastatic lung disease within 45 days of surgery. However, when mice were injected after surgery with 20 μg of gp96-peptide complexes into footpads four times at weekly intervals, 80% of the immunized mice survived for over 250 days after surgery and were free of detectable lesions (see Tamura at p. 118, col. 3; Fig. 2). Tamura further shows that when mice bearing spontaneous melanoma, UV radiation-induced spindle cell carcinoma, methlylcholanthrene-induced Meth A fibrosarcoma, and colon carcinoma were treated with 20 μg of gp96-peptide complexes per subcutaneous immunization five times on alternate days, there was efficacious cancer treatment, as demonstrated by reduced tumor growth rate and prolonged survival. Sato shows that a treatment protocol consisting of subcutaneous injection of both 2.5 μg and 5 μg of gp96-peptide complexes 4, 9, 12, and 19 days after mice that have undergone bone marrow transfusion were inoculated with a syngenic leukemia cell line, is effective in treating leukemia, wherein efficacy is demonstrated by prolonged survival (see Sato at p. 1853, col. 2; p. 1854, col. 1, and Figure 2b). Yedavelli shows anti-tumor activity of 10 μg of gp96-peptide complexes injected subcutaneously three times a week for six weeks in rats that were inoculated with a prostate cancer cell line, wherein the anti-tumor activity is demonstrated by stabilization of tumor growth (see Yedavelli at p. 246, cols. 1-2; Fig. 4). Belli discloses a clinical study in which the immunogenicity and anti-tumor activity of a vaccine consisting of melanoma tumor-derived gp96-peptide complexes (HSPPC-96) was studied in stage IV metastatic melanoma human patients, wherein 5 μg or 50 μg of vaccine was administered 5 to 8 weeks after resection of tumor metastases and given at weekly intervals either intradermally or subcutaneously (see Belli at p. 4170). Two patients, one treated

subcutaneously with 5 μg of gp96-peptide complexes and the other treated subcutaneously with 50 μg of gp96-peptide complexes, exhibited complete tumor regression and three more patients had stable disease at the end of follow-up, demonstrating that 5 μg and 50 μg of gp96-peptide complexes are effective in generating an immune response and treating melanoma in humans (see Belli at pp. 4174 and 4175). Similarly, Mazzaferro describes the administration of two cycles of intradermal administration of 2.5 μg, 25 μg and 100 μg of gp96-peptide complexes to human colorectal cancer patients, wherein the site of vaccination was rotated weekly and included: anterior deltoid region, median inguinal region and subclavicular regions (see Mazzaferro at p. 3237, col. 1). The first cycle lasted one month (four injections, once a week) and started 4-6 weeks after liver resection and the second cycle consisted of four injections given at two-week intervals, starting 8 weeks after the end of the first cycle (see Mazzaferro at p. 3237, col. 1). The authors report that the frequency of patients with an increased immune response was highest for the group of subjects who received 2.5 μg of vaccine. The authors note that "[t]his may suggest, as reported in the murine system, that the lowest dose of HSPPC-96 was more immunogenic than the intermediate or high doses...." (Mazzaferro at p. 3240, col. 1). Mazzaferro also demonstrates a correlation between patients who had a measurable immune response and survival (see Mazzaferro at Fig. 4 and Table 3). The foregoing studies demonstrate that a similar dose, and in some cases the same dose, in the range of 2.5 μg to 100 μg of gp96-peptide complexes is effective in generating an immune response and treating cancer in mice, rats, and humans.

Thus, as shown by the evidence above, it is reasonable to expect that the immunosuppressive dose of hsp complexes may be similar in humans and mice because such a similarity in effective dose was shown for the immunostimulatory activity of heat shock proteins, (as was also discussed in the Amendment filed August 25, 2004 ("the 2004 Amendment") and in the concurrently filed Declaration of Dr. Srivastava) (see page 13, para. 2 of the 2004 Amendment and the Declaration of Dr. Srivastava at para. 17). Applicants are not aware of any reason why the observed similarity in effective dose between humans and mice for the immunostimulatory activity of hsp complexes should not also be true for the immunosuppressive activity of hsp complexes (see *e.g.*, Declaration of Srivastava at para. 17).

In view of the above, Applicants submit that the guidance in the specification to start within a narrow range of effective doses, *e.g.*, in the 100-200 microgram or more range (see the specification at page 31, line 30 to page 32 line 3) represents a sufficient disclosure to

enable the claimed methods, which specify a dose of "100 μg or more," for use in a mammal other than a mouse, since optimal dosages for efficacy in such other mammals should be achievable by routine experimentation starting from such guidance.

The Examiner has not explained why the disclosure is insufficient. Instead, the Examiner contends that the disclosure is too "minimal" to be enabling "for such a critical element of the claimed method" and that "the establishment of an effective dose of HSP for immunosuppression is not a matter of simply ramping up dosages until an effective dose is determined" because, in the Examiner's view, an improper dose "would as likely kill a patient in need of immunosuppression as benefit him."

Applicants submit that determining the effective dose for any particular subject (be it a mouse, a dog, or a human) within the amount set forth in the claims is within the routine skill in the art, and is in fact the type of routine experimentation that is commonly performed during preclinical testing, *e.g.*, in mammals such as mice, rats, dogs, and primates, and during clinical testing in humans. Moreover, the example described at pages 40-41 of the specification demonstrates that doses of hsp complexes too low to inhibit graft rejection were not toxic, *i.e.*, the low doses in groups 4-6 did not result in a higher incidence of mortality for the mice in those groups. These results contradict the Examiner's assumption regarding the toxicity of an improper dose (*i.e.*, as "as likely kill a patient in need of immunosuppression as benefit him").

Applicants further submit that the Examiner is improperly requiring safety and efficacy data in humans for satisfaction of the enablement requirement of 35 U.S.C. § 112. Applicants understand the Examiner to be rejecting the utility of the dose ranges described in the specification because the Examiner asserts (1) that the specification does not teach a dose high enough to be useful in humans, based on the Examiner's unsupported assumptions about extrapolation of the effective dose from the mouse data, and (2) that it amounts to undue experimentation to find the effective dose for a mammal other than a mouse because an inappropriate dose could be highly toxic. Thus, Applicants understand this rejection to be one for lack of utility under 35 U.S.C. § 101 and § 112 (see *Rasmusson v. Smithkline Beecham Corp.*, WL 1501450 at page 3 (Fed. Cir. 2005) ("the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention."). In response, Applicants note that it is improper to request evidence of safety and efficacy in the treatment of humans

to satisfy the utility requirement of sections 101 and 112. Rather, the requirement for such safety and efficacy testing is within the realm of the Food and Drug Administration (FDA), not the Patent Office. See *e.g.*, *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995)("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.")(quoting *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)). The court in *In re Brana* made clear that a finding of utility under the patent laws does not depend upon a compound's being ready for administration to humans, stating that FDA approval "is not a prerequisite for finding a compound useful within the meaning of the patent laws." Instead, the court stated that

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, *necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.* Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Id. at 1568 (internal citations omitted)(emphasis added). The court in *In re Brana* also dismissed the PTO's argument that *in vivo* tests in animals are only preclinical tests and therefore not reasonably predictive of success for treating in humans" as confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *Id.* at 1567. The Examples in Applicants' specification clearly demonstrate that the claimed dose of "100 μg or more" exhibits the desired property of inhibiting graft rejection in a standard animal model. Accordingly, Applicants maintain that the specification is sufficient to enable the claimed methods.

In view of the above, Applicants submit that the Examiner's requirement for evidence of safety and efficacy in humans is improper under either 35 U.S.C. § 101 or § 112, first paragraph, and respectfully request that this rejection be withdrawn.

3.5. Enablement with Respect to Requirement for High Dose hsp at Time of Filing

The Examiner alleged that the discrepancies between the conclusions of the Chandawarkar 1999 reference and the Chandawarkar 2004 reference show that importance of the immunizing dose of antigen, *i.e.*, the importance of high dose hsp to achieve

immunosuppression, and that this was not understood at the time of filing (see the Office Action, p. 5, para. 5).

In response, Applicants submit that the Examiner's allegations are countered by the plain language of the specification, regardless of one's interpretation of the Chandawarkar references. The specification clearly contemplates the importance of high dose hsp for immunosuppression, *e.g.*, at page 31 line 31 to page 32 line 3, which states that:

> As demonstrated in the examples in Sections 6 and 7, below, an effective dose for prevention of graft rejection in mice is 100 μg and 200 μg gp96 subcutaneously for mice of average mass 20-25 g. These amounts of hsp (100-200 μg range) are high compared to the relatively small amounts of hsp-peptide complex that are required to elicit an effective immune response against an antigenic peptide, such as a complexed tumor antigen. Similar high doses of 100-200 μg, or more than 200 μg, of hsp may also be effective in treatment of larger mammals, including humans.

Moreover, as specifically pointed to by the specification in the text quoted above, the results of the working example demonstrate that only such high doses of gp96 are immunosuppressive (see *e.g.*, the specification at p. 41, lines 11-19). Given the express teaching in the specification that high dose hsp is effective for immunosuppression, and the working example which provides specific technical data supporting the efficacy of high dose hsp, Applicants maintain that the specification is enabling for the claimed methods as amended, which specify a dose of 100 μg or more. "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). Applicants submit that the Examiner has not come forward with any specific reason as to why this teaching in the specification is not enabling, and therefore the Examiner has failed to establish a *prima facie* case of lack of enablement.

Regarding the Examiner's contention at page 5, para. 5, of the Office Action that "Applicant cannot submit post-filing references in an attempt to enable that which was not enabled at the time of filing . . ." Applicants respectfully point out that the Chandawarkar 2004 reference and the Kovalchin reference are submitted to establish the truth of statements in the specification, which is a proper use of post-filing evidence. See *In re Brana* at 1567

n.19 (stating that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." (internal citations omitted)). Specifically, Applicants submitted the Chandawarkar 2004 reference to establish that the immunosuppressive activity of hsp is not dependent on the tissue source from which it is purified (see *e.g.*, the specification at p. 38-39), consistent with the breadth of the claims as filed which do not specify any particular tissue source in the independent claims. Accordingly, Applicants' use of post-filing evidence was proper.

The Examiner also acknowledged the limitation in the claims that the hsp is administered *after* the graft (referring, Applicants assume, to claim 54 and its dependent claims), but further stated that "the new limitation applies to only half the claims" (Office Action at page 6, para. 3). However, in the "other half of the claims," *i.e.*, claim 55 and its dependent claims, the hsp is administered after pre-treatment with donor-derived tissue and before the graft. Applicants maintain that the specification is fully enabling for claim 55 and its dependent claims. For example, at page 37, lines 13-39, the specification teaches that the graft recipient may be pre-treated, prior to transplantation, with a tissue sample obtained from the donor, and that the hsp is administered after this pre-treatment but prior to the graft. The Examiner has not come forward with any specific reason as to why this teaching in the specification is not enabling, and therefore the Examiner has failed to establish a *prima facie* case of lack of enablement. Moreover, the post-filing evidence provided by Kovalchin substantiates Applicants' claim that the methods of claims 54 and 55 are each enabled. For example, Kovalchin shows that gp96-peptide complexes are immunosuppressive when administered after the graft, which is the order set forth in claim 54 (Kovalchin at p. 182, section 3.1). Regarding claim 55, the specification teaches that pre-treatment of the recipient with a sample of donor tissue and heat shock protein can be used "to exploit the ability of hsps to specifically suppress an activated immune response" and that thus, "the recipient may be pre-treated, prior to transplantation, with a tissue sample obtained from the donor organ" (specification at p. 37, lines 13-19). It is clear from the specification that the "activated immune response" is a specific immune response against alloantigen(s) of the graft elicited by pre-treatment with the donor tissue (see the specification at p. 36, lines 31-36, and p. 37, lines 13-39). As noted by Kovalchin, the secondary graft model described in section 3.2 of Kovalchin, in which female mice primed to male antigen and then given high dose gp96

showed effective suppression of graft rejection, "supports the observation that an ongoing immune response is needed before high dose gp96 treatment could suppress" the immune response (Kovalchin at p. 184, col. 1, last sentence to col. 2 second sentence). This is consistent with the teachings in Applicants' specification that form the basis for the method of claim 55.

In view of the preceding remarks, Applicants submit that claims 54-69 satisfy the enablement requirements of 35 U.S.C. §112, first paragraph, and respectfully request that this rejection be withdrawn.

4. THE REJECTION UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

The Examiner rejected claims 55, 57, 58, 61, 63, and 70 under 35 U.S.C. §102(b) as allegedly anticipated by Srivastava *et al.*, "Tumor rejection antigens of chemically induced sarcomas of inbred mice," *Proc. Natl. Acad. Sci. U.S.A.* 83:3407-3411 (1986) ("Srivastava").

In response, Applicants respectfully submit that Srivastava fails to anticipate the claimed methods. In order to anticipate the claimed invention, a single reference must teach each and every element of the claims. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628 (Fed. Cir. 1987). Srivastava teaches that cytosol and membrane preparations derived from carcinogen (methylcholanthrene)-induced tumors growing in mice contain tumor rejection antigens ("TRAs") such that immunization of mice with these preparations, or with a purified TRA (later identified as gp96) was effective to protect the mice against subsequent challenge with live tumor cells (see Srivastava, Abstract, and p. 3407, last para. to p. 3408, first para. (tumor cells used for challenge were grown *in vivo* in the case of Meth A) and Fig. 1 at p. 3408 and Fig. 4 at p. 3410). Srivastava also shows similar results with TRA purified from CMS5 cells (another mouse sarcoma, see Srivastava at p. 3410, Fig. 4). The method disclosed by Srivastava comprises administering the cytosolic or membrane preparations or purified TRA before challenge with live tumor cells (see Srivastava at p. 3407, col. 2, para. 8, entitled "Tumor Rejection Assays"). Srivastava further teaches that the observed tumor immunity was only effective within a limited dosage range of TRA and that higher doses of TRA caused enhancement of tumor growth (see Figure 5 at p. 3410 and accompanying discussion).

Srivastava fails to anticipate independent claim 55 because Srivastava does not teach each and every element of the claim. Specifically, Srivastava does not teach the following italicized elements of claim 55: (1) administration to a mammal *in need of inhibiting graft*

rejection of a composition comprising purified complexes, each complex consisting essentially of a heat shock protein non-covalently bound to a peptide, and (2) the method further comprising *administering to the mammal a sample of cells or tissue obtained from the cells, tissue, or organ donor prior to administration of the composition.*

First, Applicants maintain their position that claim 55 is novel over the method of Srivastava because Srivastava does not teach a method of inhibiting rejection of grafted cells, tissue, or organ in a mammal *in need of* inhibiting such graft rejection. Instead, in Srivastava the mice to which the tumor cells were administered were objectively in need of rejection of these tumor cells. The Examiner's position to the contrary is based upon his assertions that either the "animals were in need of determining the results of the experiment" or were not in need at all because "experimental mice are ultimately killed after these sorts of experiments." The Examiner's reasoning does nothing to overcome the fact that the animals to which the hsp complexes were administered according to the method of Srivastava were <u>not</u> *in need of* inhibiting rejection of a graft, as specified by claim 55. Thus, the method of Srivastava is not practiced by administering to the subject specified in the instant claims, and Srivastava therefore fails to anticipate the claims. See *Jansen v. Rexall* 342 F.3d 1329, 1333 (Fed. Cir. 2003)(stating that where "the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' . . . the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, *it is a statement of the intentional purpose for which the method must be performed.*") (internal citations omitted) (emphasis added). See also *Rapoport v. Dement* 254 F.3d 1053, 1061-62 (Fed. Cir. 2001) (rejecting the argument that the count, '*A method for treatment of sleep apneas* comprising administration of a therapeutically effective amount of a Formula I azapirone compound or a pharmaceutically effective acid addition salt thereof to *a patient in need of* such treatment . . .' was anticipated on the ground that a prior art reference disclosed that a form of the compound recited in the claim could be administered, not for treatment of sleep apnea itself, but for treatment of anxiety and breathing difficulty, a symptom of apnea, stating, "[t]here is no disclosure in the [prior art reference that the compound] is administered to patients suffering from sleep apnea with the intent to cure the underlying condition" and that none of the patients to which the compound was administered were reported as suffering from sleep apnea) (emphasis added).

Second, Srivastava does not teach a method wherein a sample of cells or tissue from the donor is administered to the recipient prior to the hsp and before the graft, as specified by claim 55. Instead, where Srivastava teaches the use of purified TRA (*i.e.*, gp96), the TRA is administered prior to the graft (or "tumor challenge" in the lexicon of Srivastava) and there is no step of pre-treatment with donor tissue before administration of the TRA (see *e.g.*, Srivastava at p. 3407, col. 2, para. 8).

In view of the above remarks, Applicants submit that claims 55, and its dependent claims, satisfy the requirements of 35 U.S.C. §102(b) and respectfully request that this rejection be withdrawn.

5. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

The Examiner rejected claims 54-71 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that this is a new matter rejection.

Applicants maintain that claims 54-56 are fully supported by the specification, for the reasons set forth below.

Claim 54 as amended recites the following:

Claim 54:

> A method of inhibiting rejection of grafted cells, tissue, or organ in a mammal in need thereof comprising administering to the mammal a dose, effective to inhibit graft rejection, of a composition comprising purified complexes, each complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, wherein the heat shock protein is a member of the hsp90 family of heat shock proteins, and wherein the composition is administered after the cells, tissue, or organ is grafted to the mammal, and wherein the amount of the complexes present in the composition is 100 μg or more.

The Examiner stated that the specification at pages 11 and 31 cited to by Applicants supports only "a method of treating or preventing graft rejection or eliciting immune tolerance wherein the composition is administered after the grafted cell, tissue, or organ."

With respect to the claim term "method of *inhibiting* rejection," Applicants cited to the specification at page 10, lines 26-29, and page 11, lines 25-30, which recite methods of

"treating or preventing graft rejection" rather than "inhibiting" graft rejection. However, Applicants submit that the claim language "inhibiting" graft rejection is merely a clarification that "treating or preventing" graft rejection is by way of inhibiting rejection of the graft, as shown in the Examples in the specification and as stated in the specification, *e.g.*, at p. 36, lines 23-25 (referring to the Examples, "[t]he administration of hsp effectively *inhibited* graft rejection . . ."); at p. 38, lines 27-29 ("[t]he example detailed below, referred to herein as Example 1, demonstrates the effectiveness of the heat shock protein gp96 in *inhibiting* graft rejection"); and at p. 39, lines 33-34 (referring to the results of Example 1, "[g]raft rejection was most effectively *inhibited* in the mice of group 2 . . ."). Applicants submit that the claim term "inhibiting" does not introduce any new matter over the terms "treating or preventing" in the specification because it is clear in view of the specification that "inhibiting" is contemplated in the usage of "treating or preventing."

Applicants note that the subject matter of a claim need not be described literally, *in haec verba*, in order for the disclosure to satisfy the written description requirements of 35 U.S.C. §112, first paragraph. See *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue."). What is required is that the description clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) ("*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question."). Here, the specification reasonably conveys to those skilled in the art that the inventors had possession of "inhibiting" graft rejection.

The Examiner further stated that the specification at pages 4 and 36 teaches only the administration of hsps, not the administration of the compositions comprising purified complexes recited in the claims. In response, Applicants submit that the specification broadly supports compositions comprising the purified complexes of the invention, see *e.g.*, the specification at page 12, lines 5-8 and at page 33, lines 6-19.

Claim 55 as amended recites the following:

Claim 55:

A method of inhibiting rejection of grafted cells, tissue, or organ in a mammal in need thereof comprising administering to the mammal a dose, effective to inhibit graft rejection, of a composition comprising purified complexes, each complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, and wherein the heat shock protein is a member of the hsp90 family of heat shock proteins, the method further comprising administering to the mammal a sample of cells or tissue obtained from the cells, tissue, or organ donor prior to administration of the composition, and wherein said composition is administered prior to the cells, tissue, or organ being grafted to the mammal, and wherein the amount of the complexes present in the composition is 100 μg or more.

The Examiner stated that the pages of the specification cited to by Applicant support only a method of administering donor tissue prior to the administration of hsps, *i.e.*, that there is no support for administration of cells or organs, or for administration of the purified complexes of the claims.

Applicants respectfully note that the claim does not recite the administration of organs, but rather of "cells or tissue" *obtained from* donor cells, tissue, or organ. Applicants maintain that the specification fully supports a method comprising *administering to the mammal a sample of cells or tissue* obtained from the cells, tissue, or organ donor prior to administration of the composition as specified by claim 55. The specification at page 4, lines 26-29, states that "the invention encompasses administration of donor tissue sample prior to administration of heat shock protein and subsequent transplantation or grafting." The specification at page 37, lines 16-23, states that in a specific embodiment, "the recipient may be pre-treated, prior to transplantation, with a tissue sample obtained from the donor organ" and that "[e]xamples of such pre-treatment tissue include, but are not limited to, small portions of the actual tissue or organ to be transplanted," i.e., cells. Thus, the specification expressly supports administering a sample of donor tissue, which includes "small portions" of the tissue or organ to be transplanted. Applicants submit that it would be clear to the skilled artisan that tissues and organs are composed of cells and that the methods taught in the specification generally apply to transplantation of cells as well as tissues and organs. Thus, since "small portions" of a tissue constitute cells, the administration of "cells" is supported by the cited portions of the specification. See *e.g.*, *In re Alton*, 76 F.3d 1168, 1175, (Fed. Cir. 1996) ("If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the

claims is not explicitly described in the specification, then the adequate written description requirement is met."). What is required is that the description clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) ("*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question.").

With respect to administration of the purified complexes of the claims, Applicants submit that the specification broadly supports compositions comprising the purified complexes of the invention, see *e.g.*, the specification at page 12, lines 5-8 and at page 33, lines 6-19.

Claim 56, which has been cancelled, recited the following:

Claim 56:

> The method of claim 54 or 55, wherein the amount of the complexes present in the composition is 100 μg or more.

The recitation of claim 56 now appears in claims 54 and 55. The Examiner alleged that the specification does not disclose administration of 100 micrograms or more of the complexes. Applicants submit that the teaching in the specification that an effective dose is "100-200 μg, or more than 200 μg" (see the specification at p. 32, lines 1-2) provides support for the claimed limitation of "100 μg or more" because it would be abundantly clear to one skilled in the art that the invention encompasses all the specific embodiments taught in the specification. Thus, taking together the embodiments of "100-200 micrograms" and "more than 200 micrograms" it would be clear to the skilled artisan that the invention encompasses the embodiment of "more than 100 micrograms." By way of further explanation, if a genus encompasses X to Y (where Y is greater than X), as well as more than Y, the genus must encompass more than X, using clear, basic mathematical principles.

In view of the above, Applicants maintain that claims 54-56 satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw the rejections under this paragraph.

CONCLUSION

Applicants believe that the present claims meet all of the requirements for patentability. An allowance of the application is earnestly requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

By: T.C. TSANG 40,258

Date: January 29, 2007

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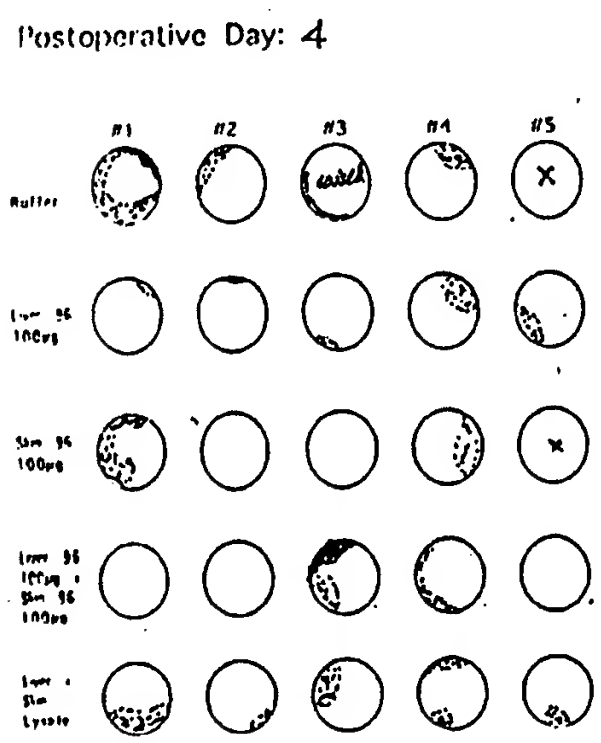
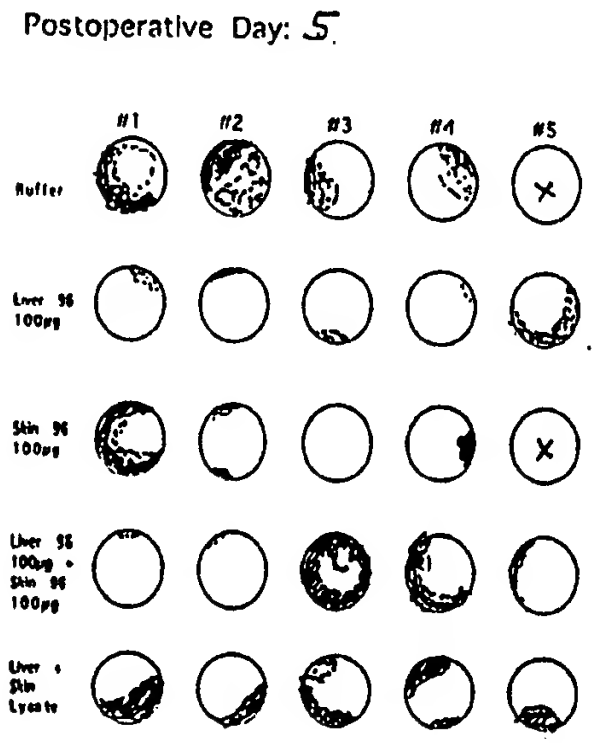
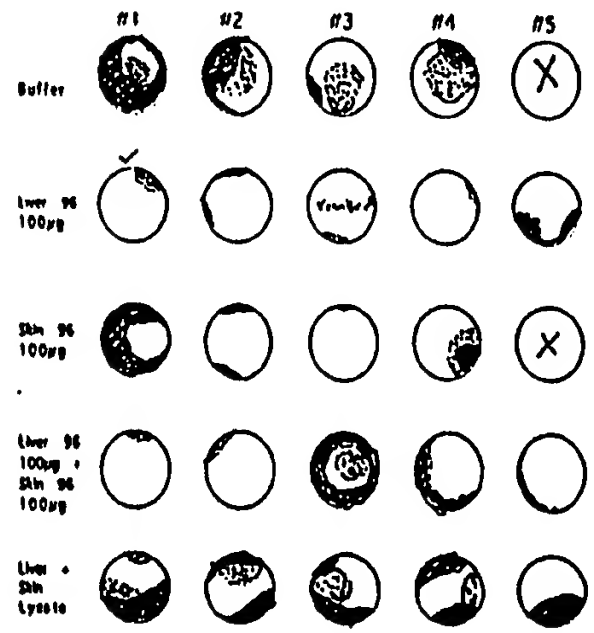
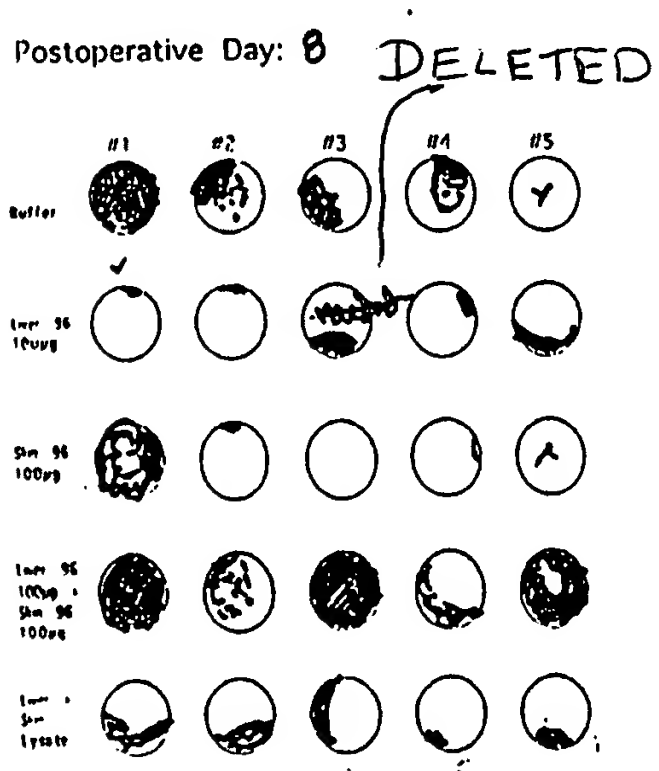
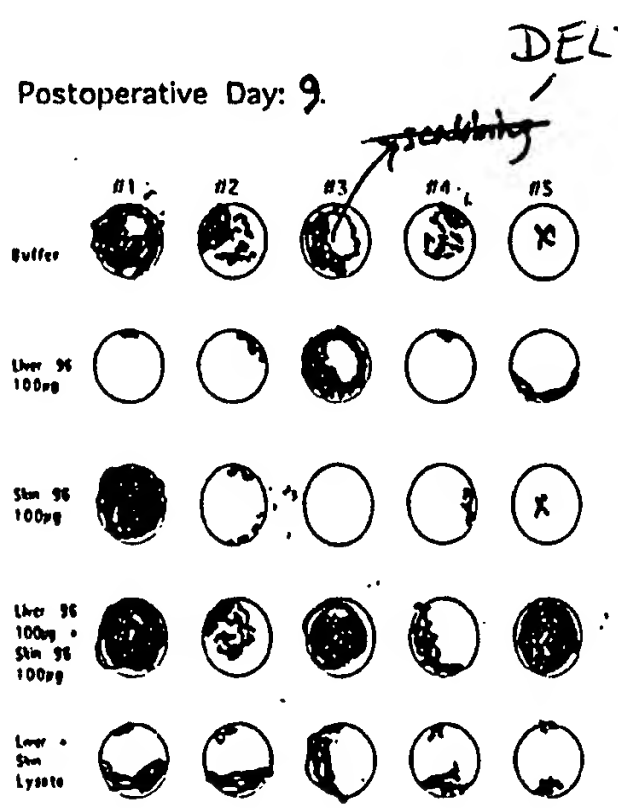
FIG. 1

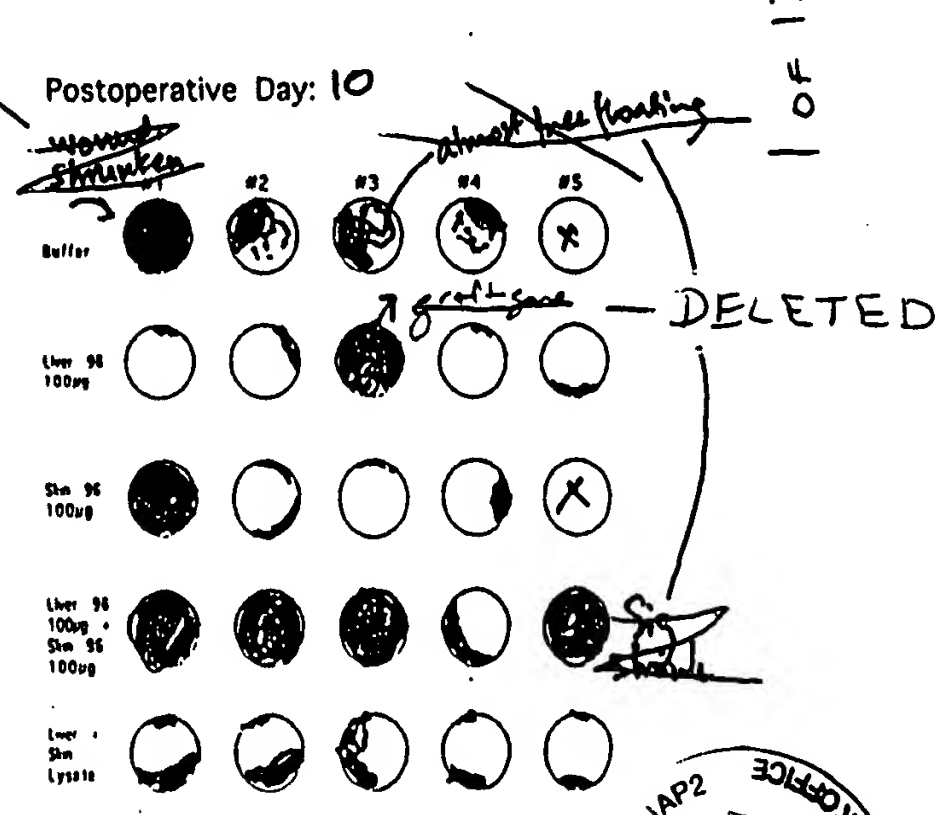












HANDWRITTEN NOTES DELETED

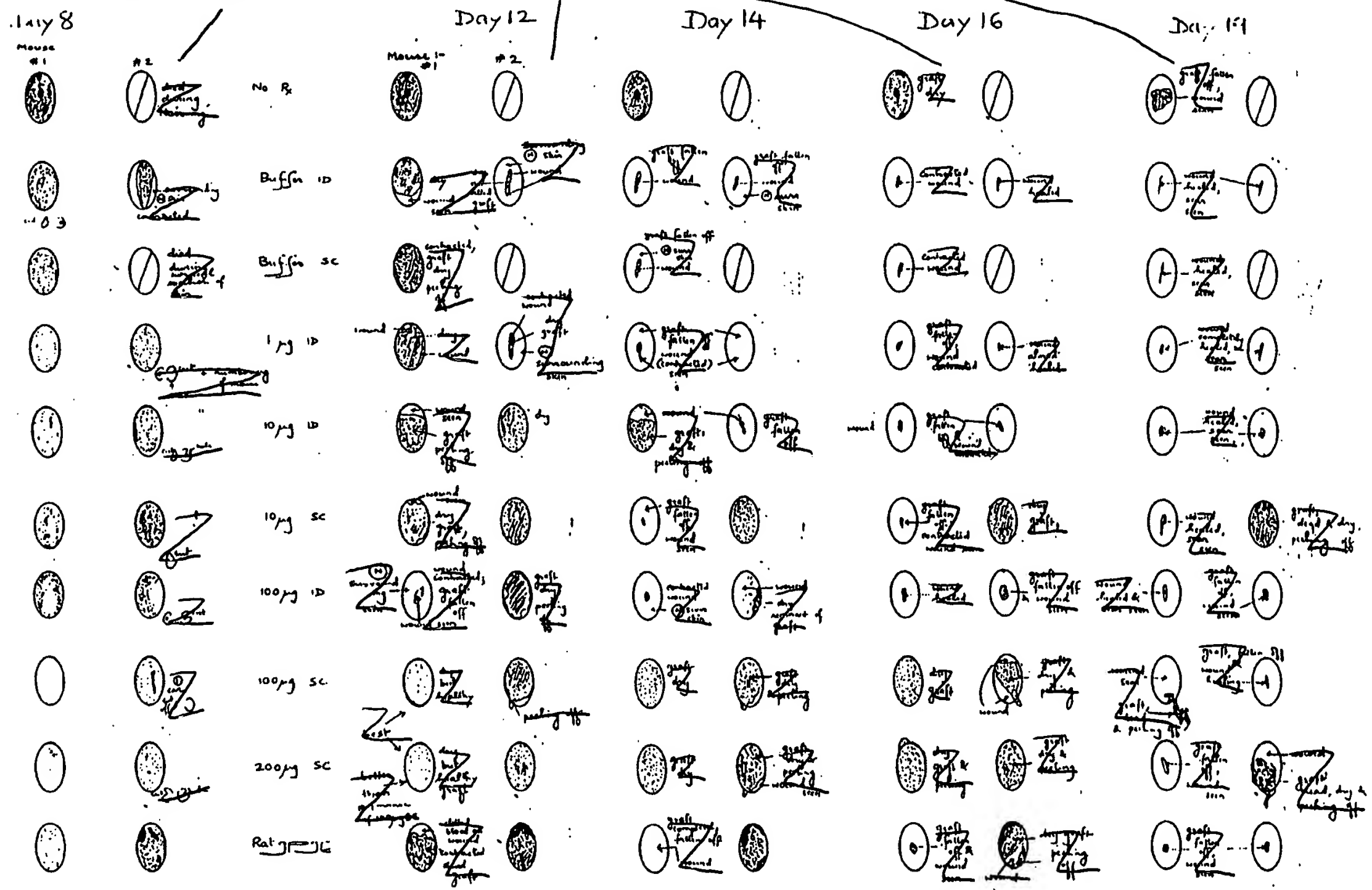


FIG. 2

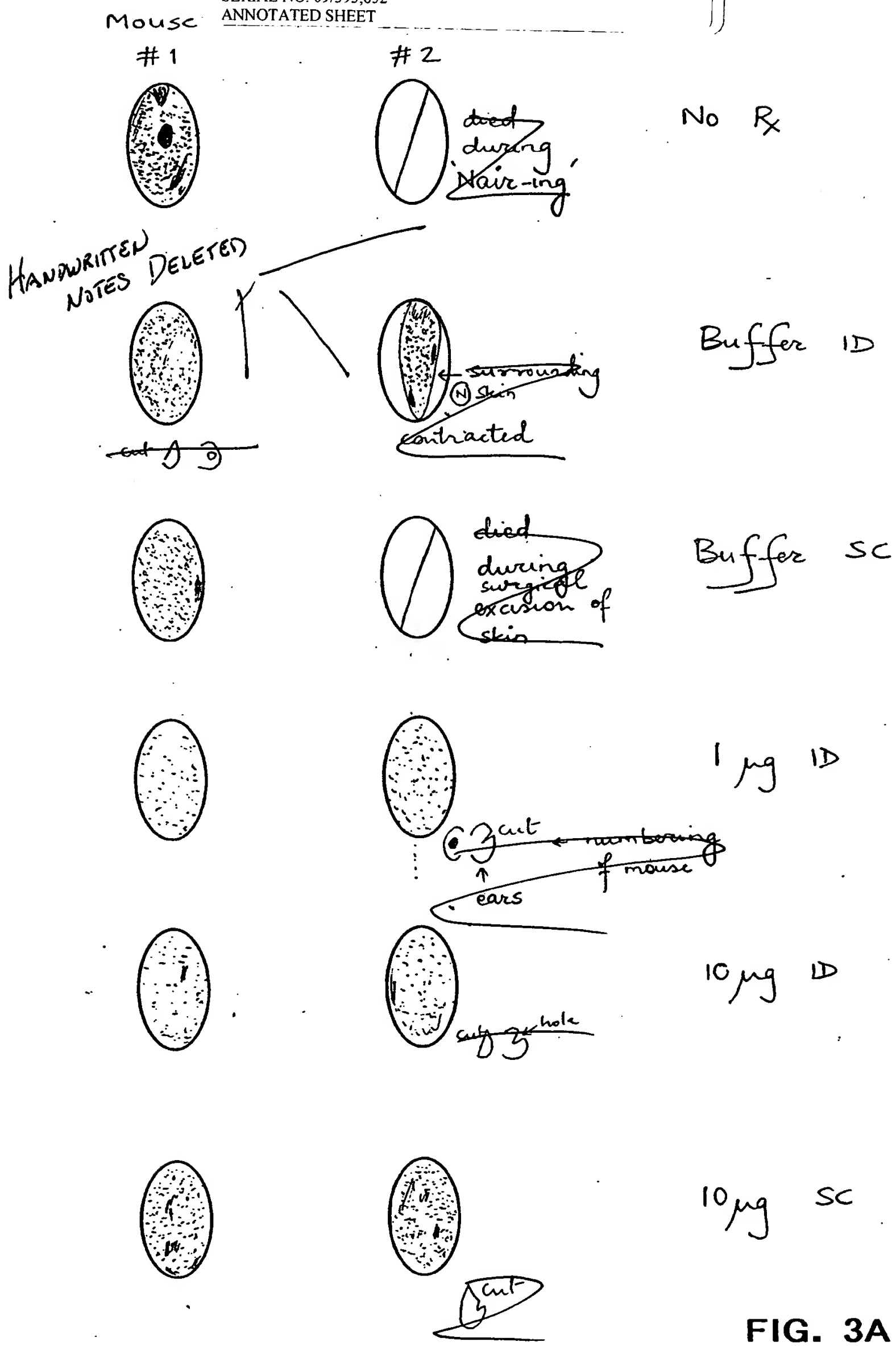

Mouse
#1
#2
died during Hair-ing
No Rx
HANDWRITTEN NOTES DELETED
surrounding
N Skin
contracted
Buffer ID
died during surgical excision of skin
Buffer SC
1 µg ID
cut
numbering of mouse
ears
10 µg ID
cut hole
10 µg SC
cut

FIG. 3A

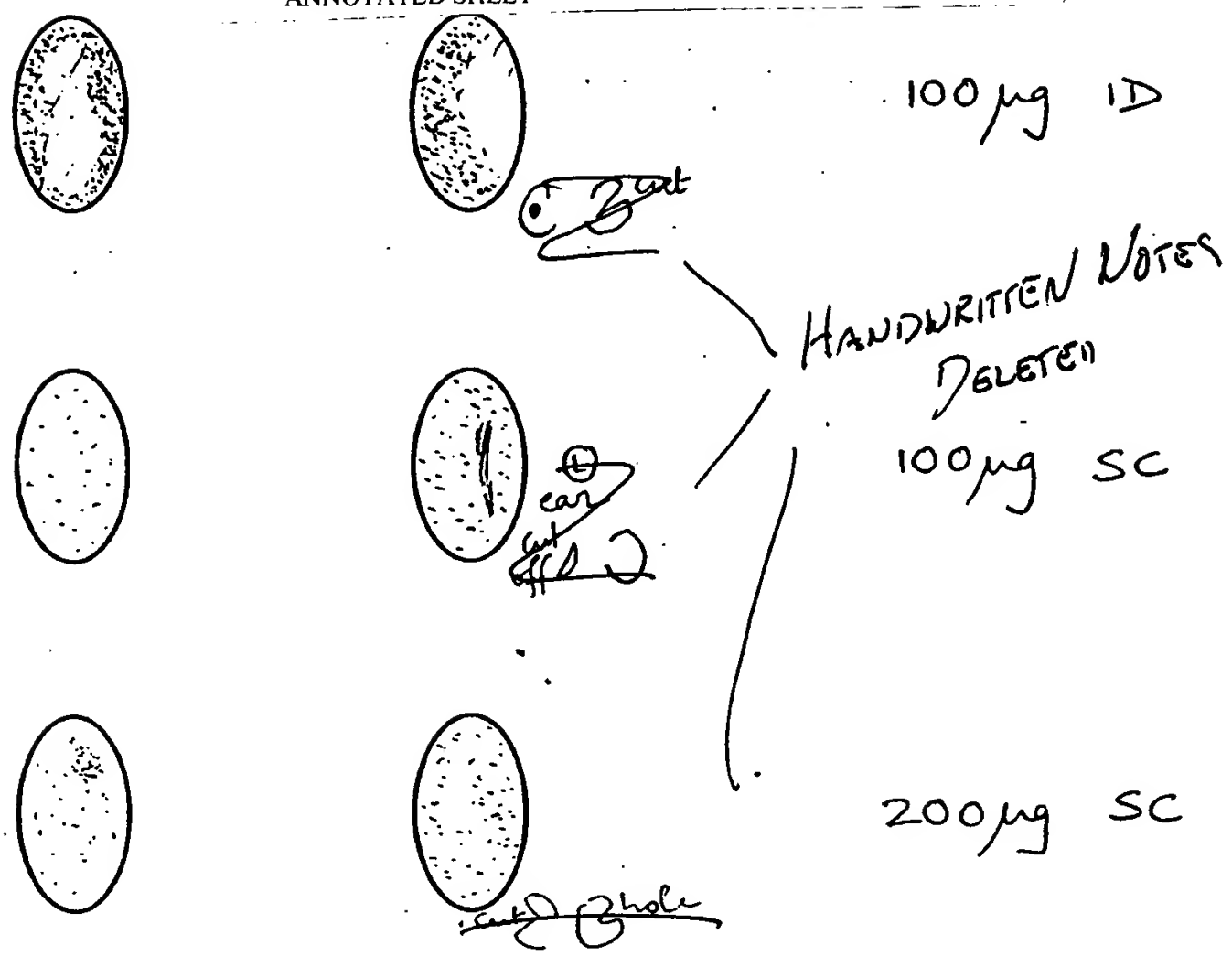

100µg ID
HANDWRITTEN NOTES DELETED
100µg SC
200µg SC
Rat gFGF 10µg ID
necrotic
haemorrhagic area
graft fallen off; underlying wound visible
healthy area
less healthy area

FIG. 3B

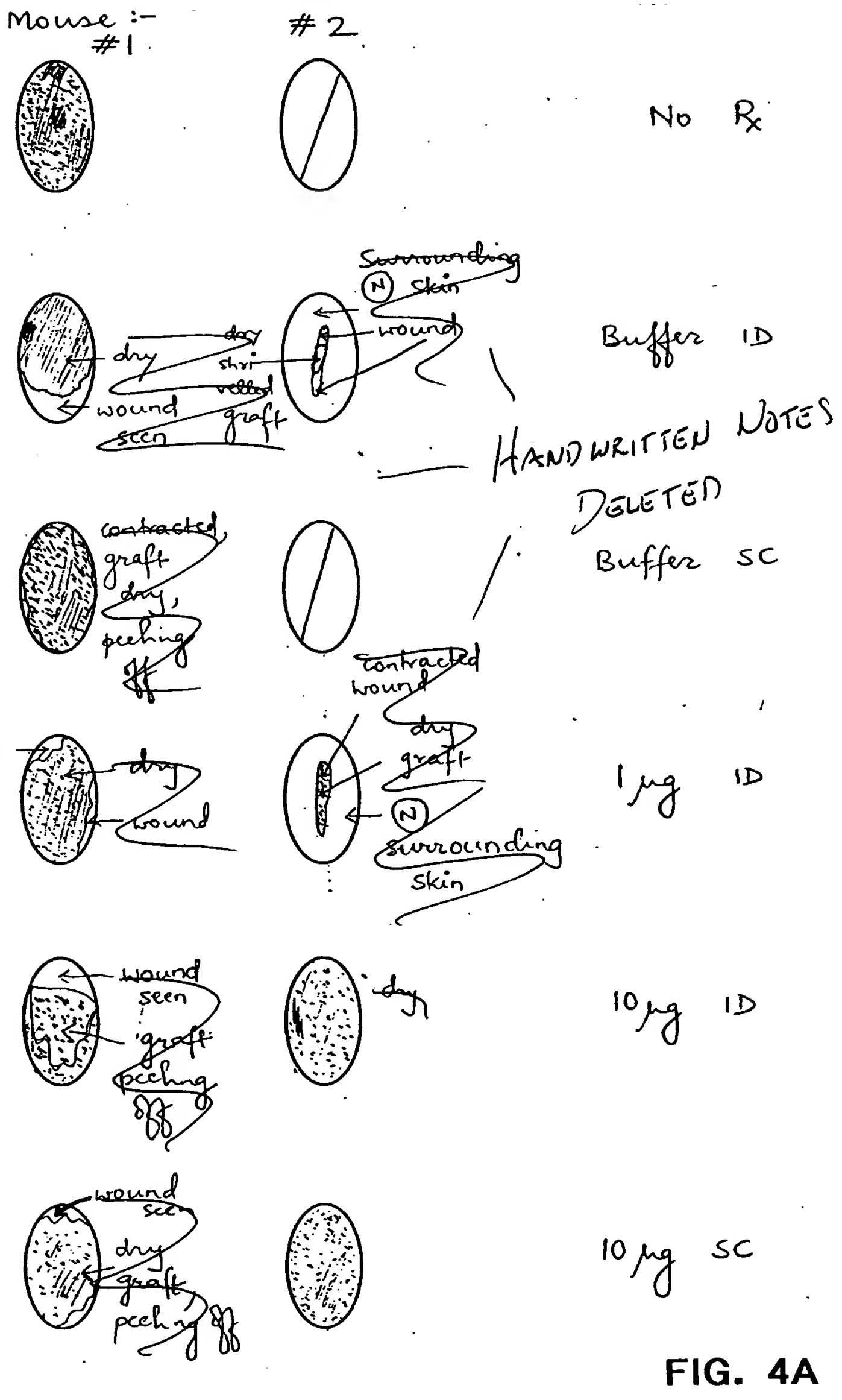

Mouse :-
#1
#2
No Rx
Surrounding
(N) Skin
wound
dry
skin
wound
graft
skin
Buffer ID
HANDWRITTEN NOTES
DELETED
Buffer SC
contracted
graft
dry,
peeling
off
contracted
wound
dry
graft
(N)
surrounding
skin
1 µg ID
wound
dry
wound
wound
seen
graft
peeling
off
dry
10 µg ID
wound
seen
dry
graft
peeling
off
10 µg SC

FIG. 4A

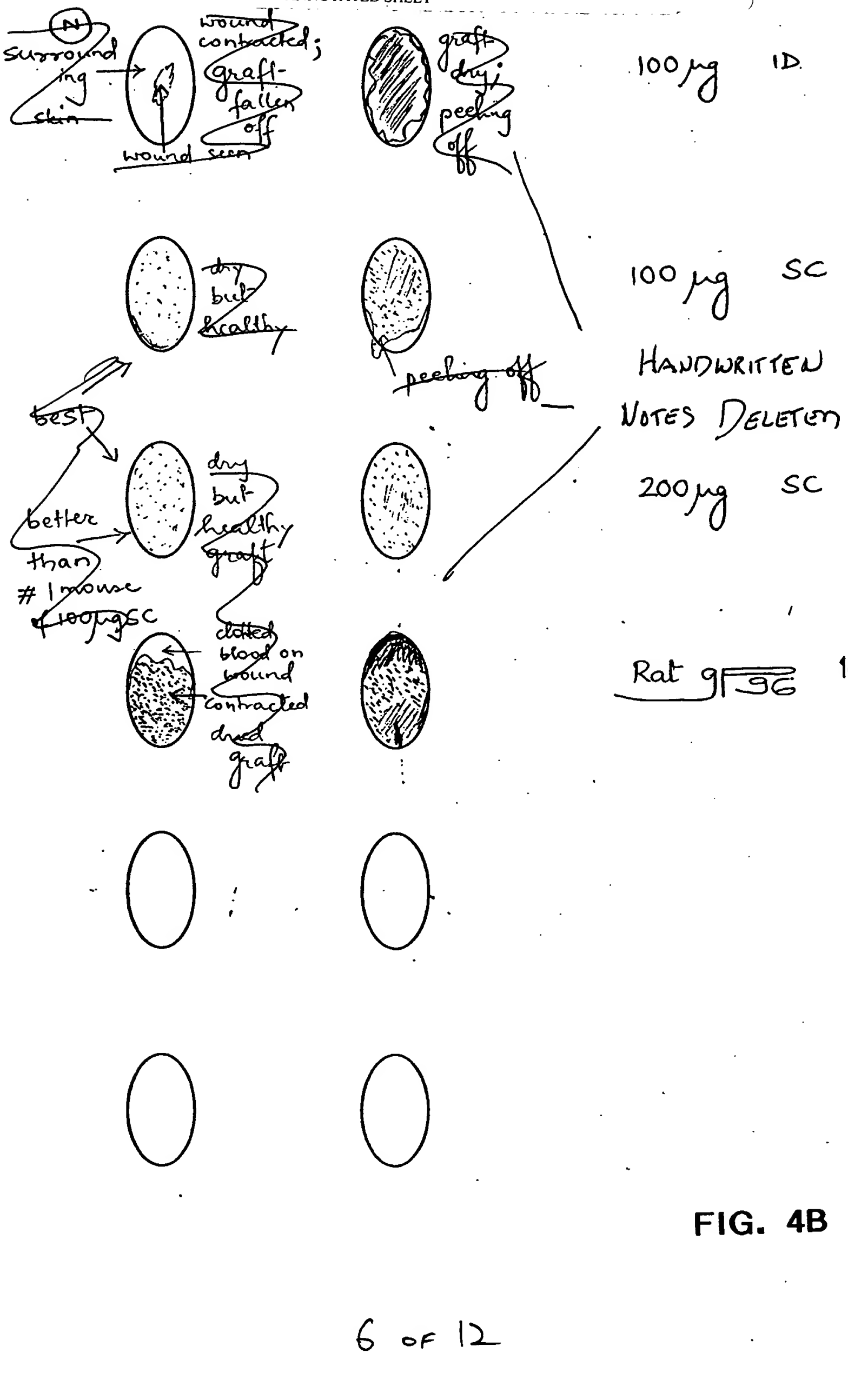

N
surrounding skin
wound contracted; graft-fallen off
wound seen
graft dry; peeling off
100 µg ID
dry but healthy
100 µg SC
peeling off
HANDWRITTEN NOTES DELETED
best
better than #1 mouse 100µg SC
dry but healthy graft
200 µg SC
clotted blood on wound
contracted dried graft
Rat 9 of 96
10 µg ID

FIG. 4B

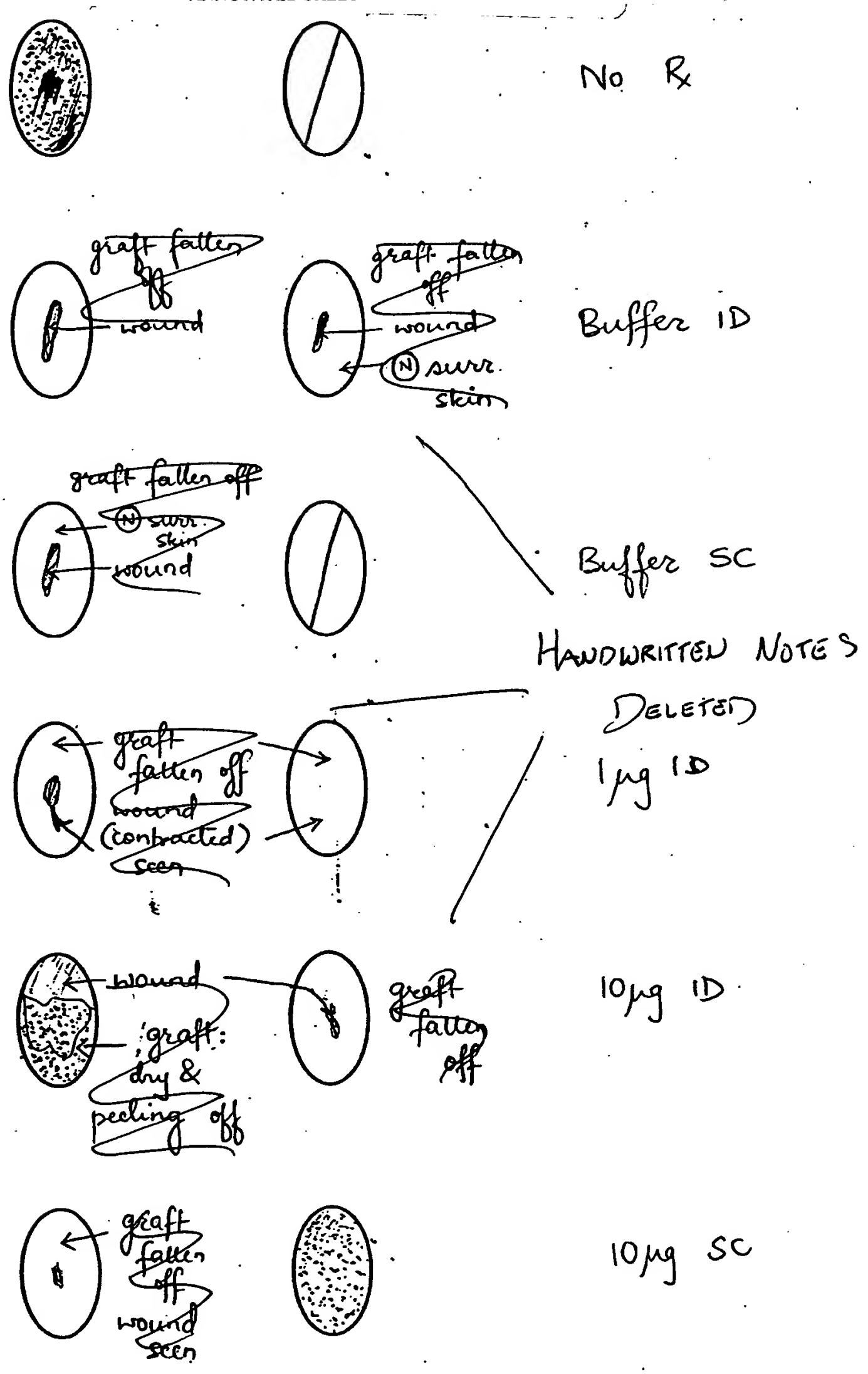

No Rx
graft fallen off
wound
Buffer ID
graft fallen off
wound
N surr. skin
graft fallen off
N surr. skin
wound
Buffer SC
HANDWRITTEN NOTES
DELETED
graft fallen off
wound (contracted)
seen
1µg ID
wound
graft: dry & peeling off
graft fallen off
10µg ID
graft fallen off
wound seen
10µg SC

FIG. 5A

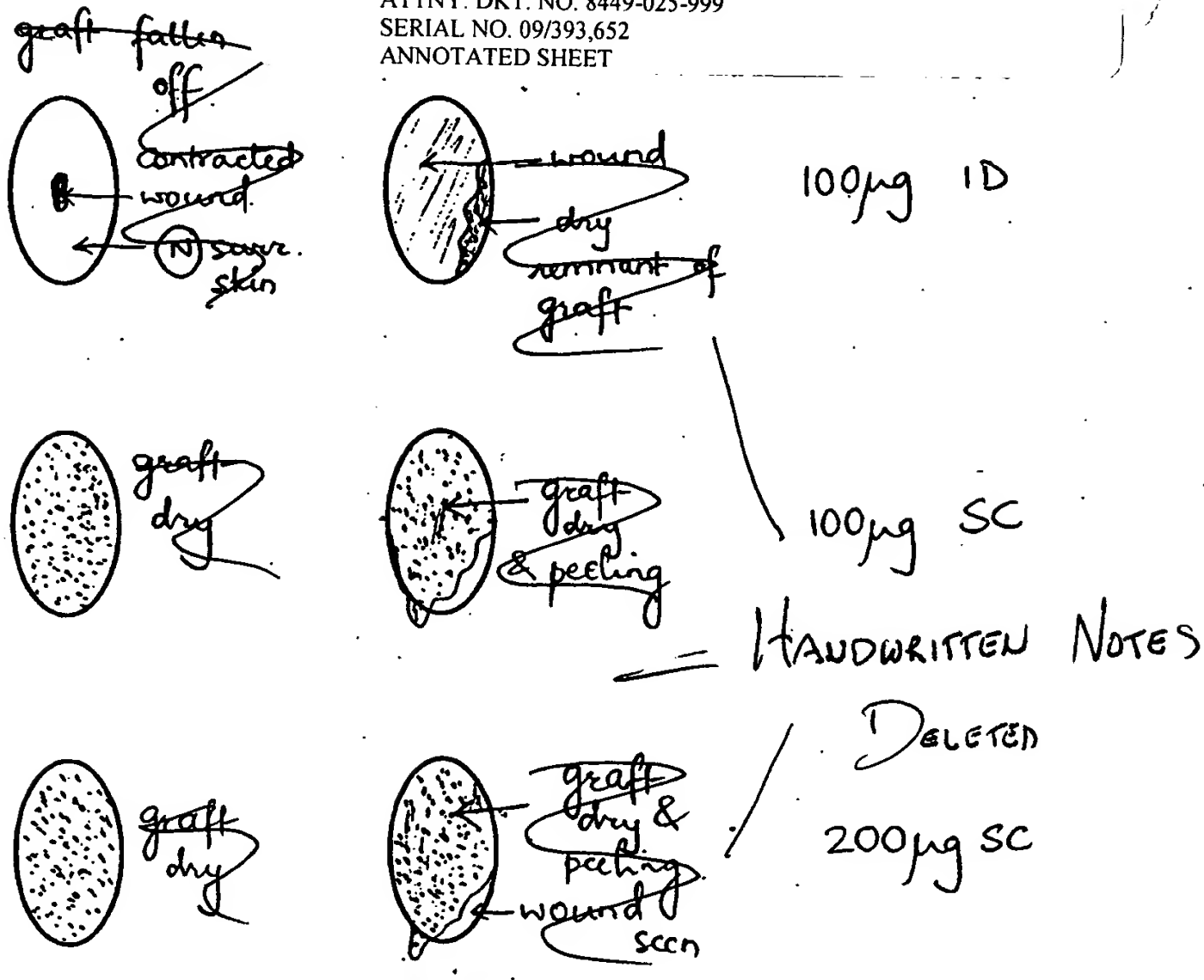

graft fallen off
contracted wound
(N) scarce skin
wound
dry
remnant of graft
100µg ID
graft dry
graft dry & peeling
100µg SC
HANDWRITTEN NOTES
DELETED
graft dry
graft dry & peeling
wound scan
200µg SC
graft completely fallen off
wound
Rat gp96 10µg ID

FIG. 5B

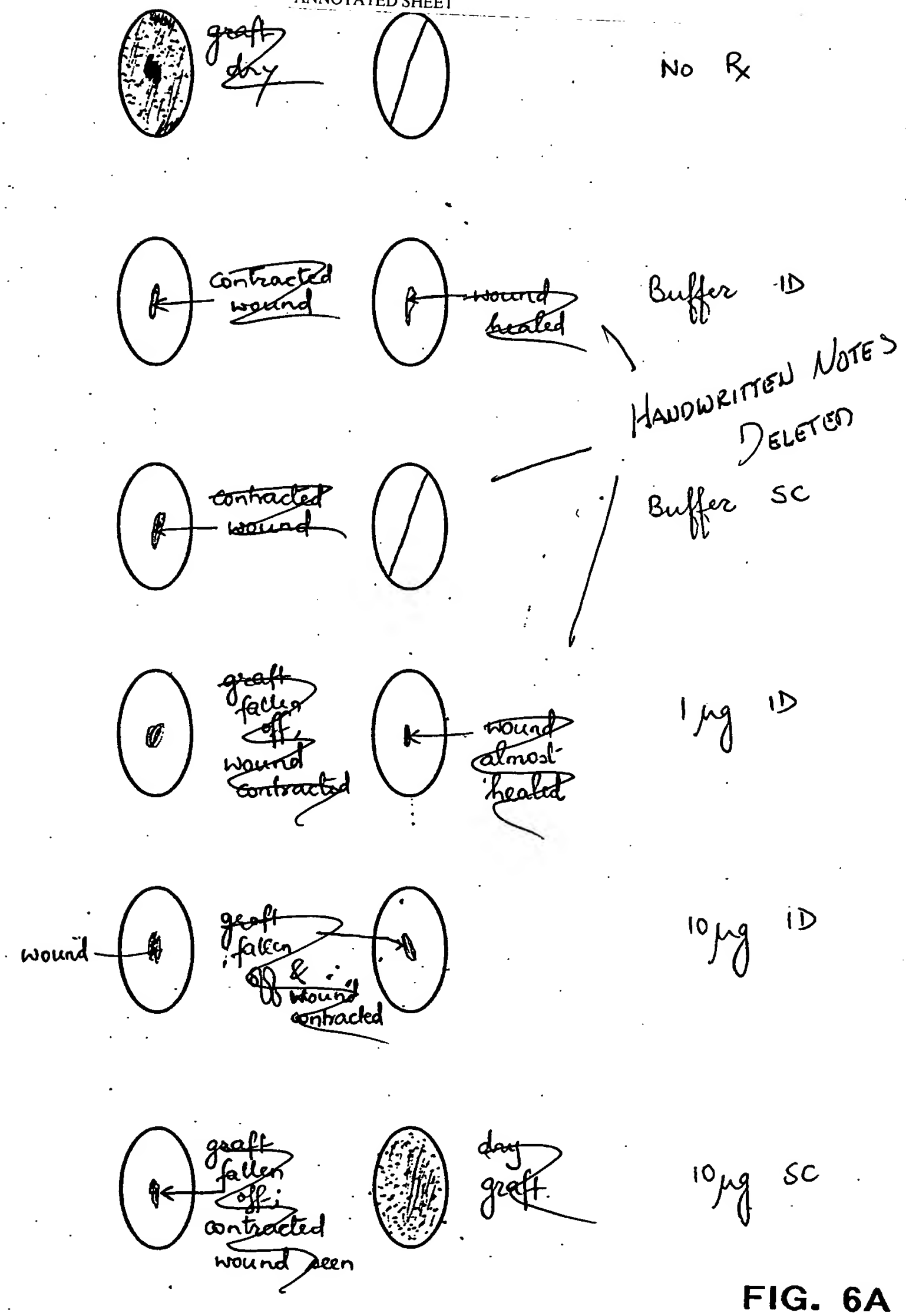

graft dry
No Rx
contracted wound
wound healed
Buffer ID
HANDWRITTEN NOTES
DELETED
contracted wound
Buffer SC
graft fallen off wound contracted
wound almost healed
1 µg ID
wound
graft fallen off & wound contracted
10 µg ID
graft fallen off contracted wound seen
dry graft
10 µg SC

FIG. 6A

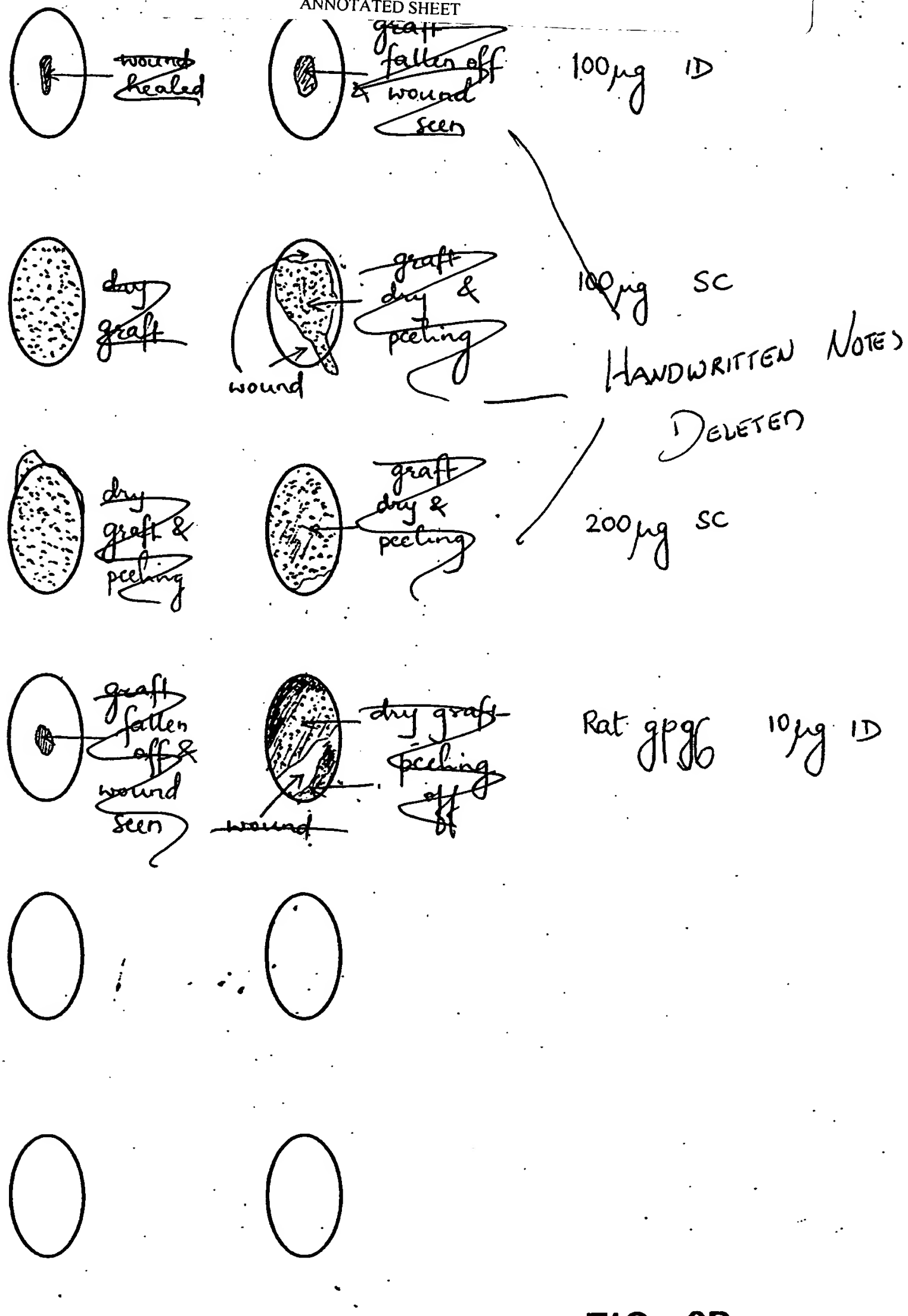

wound healed
graft fallen off & wound seen
100μg ID
dry graft
graft dry & peeling
wound
100μg SC
HANDWRITTEN NOTES
DELETED
dry graft & peeling
graft dry & peeling
200μg SC
graft fallen off & wound seen
dry graft
peeling off
wound
Rat gpgc 10μg ID

FIG. 6B

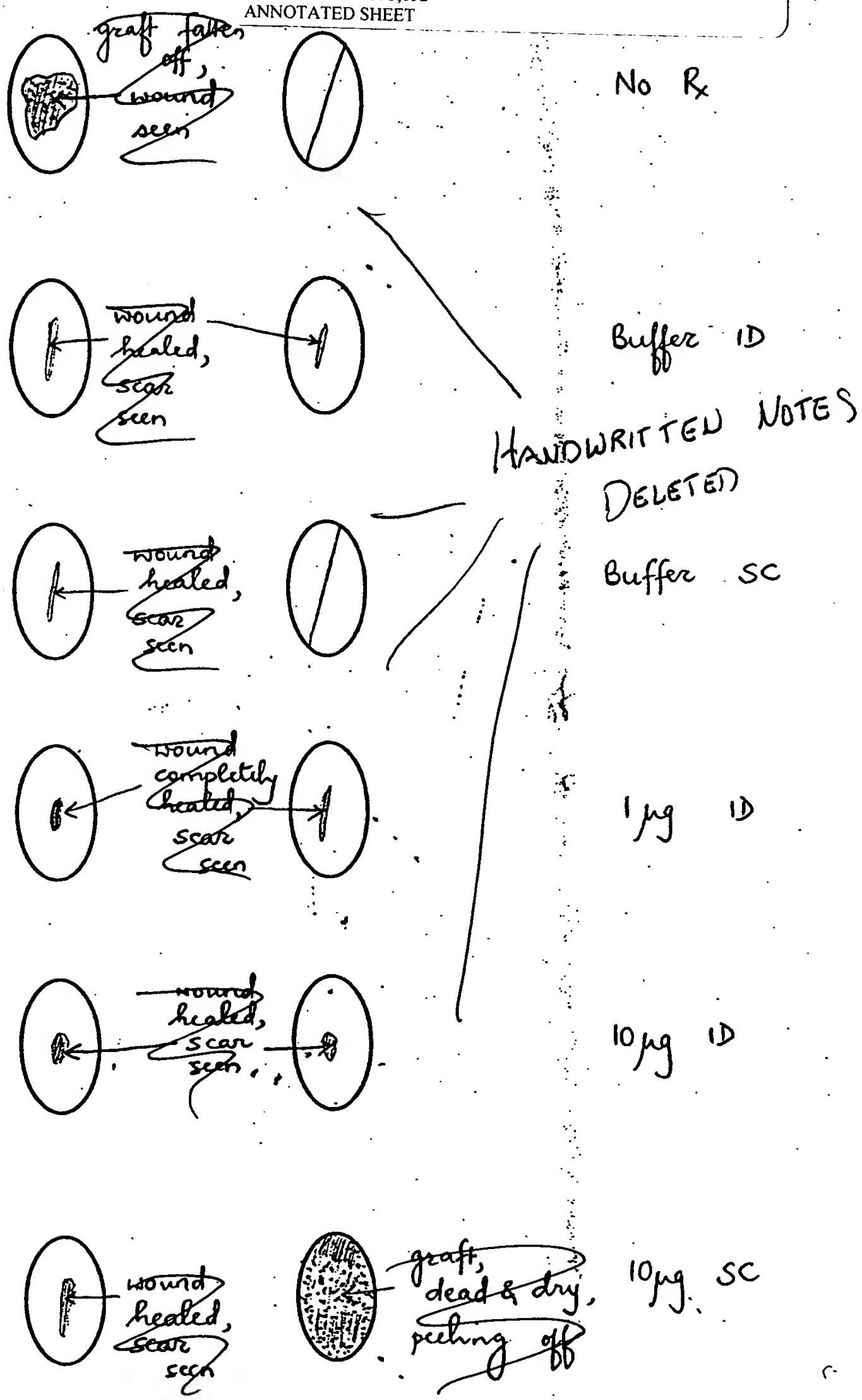

graft fallen off, wound seen
No Rx
wound healed, scar seen
Buffer ID
HANDWRITTEN NOTES
DELETED
wound healed, scar seen
Buffer SC
wound completely healed, scar seen
1 µg ID
wound healed, scar seen
10 µg ID
wound healed, scar seen
graft, dead & dry, peeling off
10 µg SC

FIG. 7A

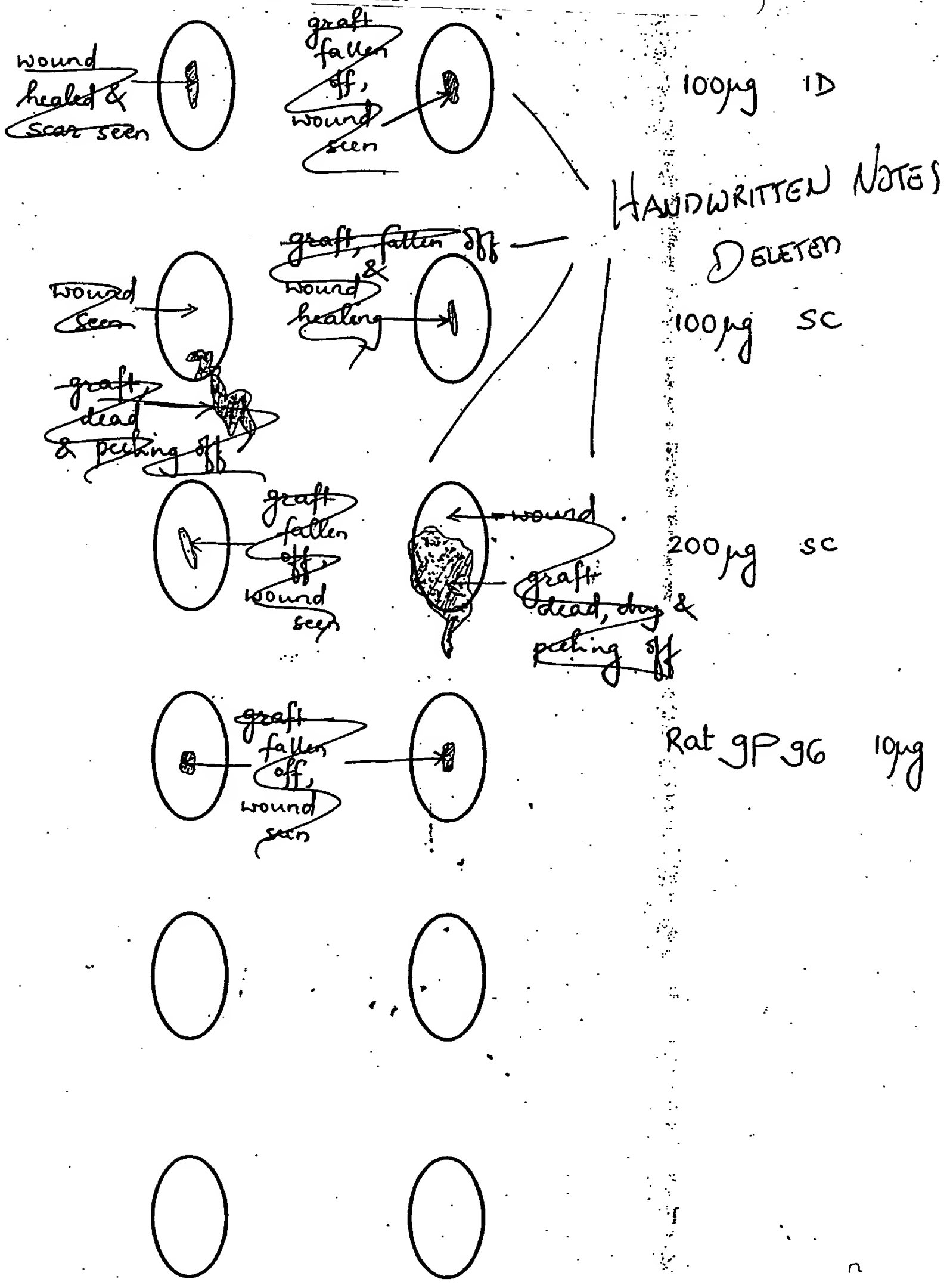

wound healed & scar seen
graft fallen off, wound seen
100µg ID
HANDWRITTEN NOTES
DELETED
graft, fallen off & wound healing
wound seen
100µg SC
graft dead & peeling off
graft fallen off, wound seen
wound
graft dead, dry & peeling off
200µg SC
graft fallen off, wound seen
Rat gp 96 10µg ID

FIG. 7B